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# Predictive Value of Initial $^{18}\text{F}$ -FLT Uptake in Patients with Aggressive Non-Hodgkin Lymphoma Receiving R-CHOP Treatment

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R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine, and prednisone)-like chemotherapy is the standard therapy in aggressive B-cell lymphoma.  $^{18}\text{F}$ -FDG PET has high prognostic implications at treatment completion but is limited as an early predictor. Here, we present the results of a prospective study correlating the initial uptake of the in vivo proliferation marker 3'-deoxy-3'- $^{18}\text{F}$ -fluorothymidine ( $^{18}\text{F}$ -FLT) with the clinical outcome of patients with aggressive non-Hodgkin lymphoma treated with R-CHOP. **Methods:** Sixty-six eligible patients were evaluated prospectively with  $^{18}\text{F}$ -FLT PET before R-CHOP. PET was performed 45 min after injection of 300–370 MBq of  $^{18}\text{F}$ -FLT. Mean and maximum standardized uptake values (SUVs) were calculated on a lesion-by-lesion basis. Response was assessed at the end of therapy. International Prognostic Index (IPI) scores and clinical parameters (Ann Arbor stage, lactate dehydrogenase, performance status, extranodal disease) were determined in all patients. Response was assessed according to revised response criteria after the end of therapy. After treatment, patients were followed in intervals from 4 wk to 6 mo (mean follow-up, 23.1 mo [range, 1–63 mo]), and progression-free and overall survival were determined. **Results:** All lymphoma lesions identified by a reference method ( $^{18}\text{F}$ -FDG PET/CT or multislice CT of the trunk) showed increased focal tracer uptake (mean  $^{18}\text{F}$ -FLT SUV,  $7.3 \pm 2.5$ ). Response assessment revealed progressive disease in 4, partial response in 3, and complete response (CR) in the remaining 55 patients. The IPI score was predictive for achieving CR ( $P = 0.034$ ). Importantly, initial mean SUV was also significantly higher in patients who showed progressive disease and partial response than in patients who achieved CR ( $P = 0.049$ ). In addition, we found a significant correlation between IPI score and initial  $^{18}\text{F}$ -FLT uptake. **Conclusion:** Taken together, high  $^{18}\text{F}$ -FLT uptake is a negative predictor of response to R-CHOP treatment in aggressive B-cell non-Hodgkin lymphoma and correlates with

the IPI score. Thus,  $^{18}\text{F}$ -FLT PET may represent a useful tool for implementing risk-adapted treatment in these patients.

**Key Words:**  $^{18}\text{F}$ -FLT; PET; lymphoma; predictive value; response

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**C**HOP (cyclophosphamide, doxorubicine, vincristine, and prednisone), or CHOP-like chemotherapy in combination with the chimeric monoclonal anti-CD20 antibody rituximab (R-CHOP), is the standard of care in diffuse large B-cell lymphoma (DLBCL) (1,2). Despite improved overall response rates, progression-free survival, and overall survival in the rituximab era, many patients do not achieve a durable remission after first-line treatment and ultimately die from the disease. Therefore, it remains crucial to identify these patients before or early in the course of treatment. Heretofore, the use of  $^{18}\text{F}$ -FDG PET has proven useful for identifying patients who have an excellent prognosis after standard treatment but has failed to accurately identify patients who would benefit from alternative treatment strategies or who should be included into clinical trials because of a dismal outcome with R-CHOP-like therapy (3,4).

Introduction of the thymidine analog 3'-deoxy-3'- $^{18}\text{F}$ -fluorothymidine ( $^{18}\text{F}$ -FLT), a PET tracer derived from the cytostatic drug azidovudine, allows in vivo imaging of proliferating tissues and malignant tumors (5). Recently, published studies demonstrated a significant correlation of tumor cell proliferation and  $^{18}\text{F}$ -FLT uptake in lymphoma and solid tumors (6–12). Preliminary studies have also shown that  $^{18}\text{F}$ -FLT PET allows noninvasive assessment of tumor grading and early response assessment (6,10). Predictive markers are desirable, guiding optimal treatment in lymphoma; yet the suitability of the initial  $^{18}\text{F}$ -FLT uptake has not been studied thus far. Therefore, the aim of this study was to correlate the initial uptake of the pro-

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liferation marker  $^{18}\text{F}$ -FLT with the clinical outcome of patients with DLBCL treated with standard R-CHOP.

## MATERIALS AND METHODS

### Patient Selection, Histology, and Treatment

Seventy lymphoma patients 18 y of age or older were referred to our center and included into this prospective trial (38 men, 32 women; mean age  $\pm$  SD,  $59 \pm 15$  y). Participation in this study was offered to all consecutive patients with aggressive B-cell lymphoma such as DLBCL or follicular lymphoma grade IIIB. During the recruitment period, an additional 15 patients would have been eligible to participate (~20% of the total study collective); however, because of the severity of clinical symptoms and limited availability of  $^{18}\text{F}$ -FLT, induction therapy had to be initiated immediately and pretherapeutic PET could not be performed.

Patients with a history of malignancies or preceding chemo- or radiotherapy were excluded. All biopsies were either performed and analyzed or reviewed at our institution by 2 independent expert hematopathologists. Ki67 immunohistochemistry was performed as previously described (13). Lymphomas were categorized according to the updated classification of the World Health Organization (14). Histopathology revealed aggressive B-cell lymphoma in 66 patients (64 DLBCLs and 2 follicular lymphoma grade IIIB), follicular lymphoma grade I in 2 patients, and anaplastic T-cell non-Hodgkin lymphoma in 2 patients (Table 1). Details of the study were explained by a physician, and written informed consent was obtained from all patients. The International Prognostic Index (IPI) scores (15) and clinical stages for all DLBCL and follicular lymphoma grade IIIB patients are shown in Table 2. A study of a subgroup of 22 patients that investigated the feasibility of repeated  $^{18}\text{F}$ -FLT PET early in the course of treatment for identifying responding patients by a significant drop of the  $^{18}\text{F}$ -FLT retention in aggressive non-Hodgkin lymphoma was published previously (10).

All eligible patients were scheduled to undergo systemic chemotherapy with R-CHOP ( $n = 66$ ).  $^{18}\text{F}$ -FLT PET was performed in all 66 patients within 4 d before treatment. Treating physicians were unaware of the findings of the  $^{18}\text{F}$ -FLT PET studies, and these results did not affect treatment decisions. The study protocol was approved by the local ethics committee of Technische Universitaet Muenchen.

### PET

$^{18}\text{F}$ -FLT was synthesized as previously described (16). Imaging was performed on a whole-body high-resolution PET scanner (ECAT HR+; Siemens/CTI). This device simultaneously acquires 47 contiguous slices with a slice thickness of 3.4 mm. The in-plane image resolution of transaxial images was approximately 8 mm in full width at half maximum, with an axial resolution of approximately 5 mm in full width at half maximum.

**TABLE 1**  
Histology of All Screened Lymphoma Patients ( $n = 70$ )

Histology	<i>n</i>
DLBCL	64
Follicular lymphoma grade I	2
Follicular lymphoma grade IIIB	2
Large cell anaplastic T-cell lymphoma	2

**TABLE 2**  
Characteristics of Eligible Patients ( $n = 66$ )

Characteristic	Value	Percentage
Age (y)		
Median	63	
Range	26–82	
Stage ( <i>n</i> )		
I	18	27
II	10	15
III	6	9
IV	32	49
IPI score ( <i>n</i> )		
0/1	24	36
2	17	26
3	14	21
4	10	15
5	1	2
Response ( <i>n</i> )		
CR	55	83
PR	3	5
PD	4	6
NA	4	6
$^{18}\text{F}$ -FLT uptake ( $\text{SUV}_{\text{mean}}$ )		
Mean	7.3	
SD	3.3	
Median	6.9	
Range	1.0–18.2	

Response could not be assessed in 4 patients (NA) because they had died early or were lost to follow-up. In 1 patient, IPI score could not be determined.

Static emission images were acquired 45 min after injection of approximately 300 MBq (range, 270–340 MBq) of  $^{18}\text{F}$ -FLT. Emission data were corrected for random coincidences, dead time, and attenuation and reconstructed by filtered backprojection (Hanning filter with cutoff frequency 0.4 cycles per bin). The matrix size was  $128 \times 128$  pixels, with a pixel size of  $4.0 \times 4.0$  mm. The image pixel counts were calibrated to activity concentrations (Bq/mL) and decay corrected using the time of tracer injection as a reference.

### PET Data Analysis

All PET scans were evaluated by 2 observers blinded to the clinical data and the results of other imaging studies. Circular 2-dimensional regions of interest with a diameter of 1.5 cm (corresponding to 10 pixels) were placed in the area with the highest tumor activity, as previously published (10). Mean standardized uptake value ( $\text{SUV}_{\text{mean}}$ ) and maximum SUV ( $\text{SUV}_{\text{max}}$ ) were calculated from each region of interest using the formula  $\text{SUV} = \text{measured activity concentration (Bq/g)} \times \text{body weight (g)} / \text{injected activity (Bq)}$ . For further analyses, mean values from both observers were used. Regions of interest were also placed in the following tissues: liver (right liver lobe, excluding the central part and the liver margins), bone marrow, and gluteal muscle. This algorithm has been demonstrated to be a valuable tool for assessing therapy response (10,17,18). For definition of regions of interest and data analysis, custom software developed at our institution in interactive data language (Research Systems, Inc.) was used.

## Reference Methods, Clinical Evaluation, and Follow-up

Diagnostic baseline CT or  $^{18}\text{F}$ -FDG PET/CT ( $n = 37$ ) of the head and neck, thorax, abdomen, and pelvis were performed within 1 wk before chemotherapy, serving as a reference for the presence of nodal or extranodal manifestation sites of aggressive lymphoma. Because  $^{18}\text{F}$ -FDG PET/CT for the detection and staging of lymphoma is not reimbursed and currently is not a standard pretreatment assessment, it is not included as a reference in all patients. From January 2007,  $^{18}\text{F}$ -FDG PET/CT was routinely performed for staging purposes in 37 of 42 recruited patients.

Patients were reevaluated using CT after 3 courses of R-CHOP and at the end of chemotherapy. Treatment response was classified as complete response (CR), partial response (PR), no change (NC), or progressive disease (PD), according to the standardized response criteria for non-Hodgkin lymphoma (19). In the case of residual lymph node enlargement,  $^{18}\text{F}$ -FDG PET was performed and analyzed according to the revised response criteria for malignant lymphoma (20). Treatment response was further evaluated according to standard protocols, including clinical evaluation, ultrasound, chest radiography, CT, and laboratory tests, every 3 mo.

## Statistical Analysis

Statistical analyses were performed at the Institute of Medical Statistics and Epidemiology at Technische Universitaet Muenchen using PASW statistics software (version 18.0; SPSS, Inc.). Quantitative values were expressed as mean  $\pm$  SD, median, and range. Related metric measurements were compared using the Wilcoxon signed-rank test, and the Mann-Whitney  $U$  test was used to compare quantitative data between 2 independent samples. To assess the prognostic impact of continuous variables with regard to survival, Martingale residual analysis was performed (21). Smoothing spline equations have been fitted to the residual plots to depict the shape of the functional relationship between the continuous prognostic variable and risk of death.

The Fisher exact test was used for comparison of frequencies, and Spearman correlation coefficients were calculated to quantify bivariate correlations of measurement data. Exact 2-sided 95% confidence intervals (CIs) were reported for estimates of sensitivity and specificity. All statistical tests were conducted 2-sided, and a  $P$  value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

### Clinical Stage and Response to Therapy

Sixty-six patients met the inclusion criteria. According to the initial staging, 18 patients (27%) presented with stage I disease. Stages II, III, and IV were found in 10 (15%), 6 (9%), and 32 (49%) patients, respectively, as indicated by the reference methods (diagnostic CT or  $^{18}\text{F}$ -FDG PET/CT). Detailed characteristics of all eligible patients are shown in Table 1. End-of-therapy assessment was available in 62 patients and indicated CR in 55 patients, PR in 3, and PD in 4. Four patients were lost to follow-up.

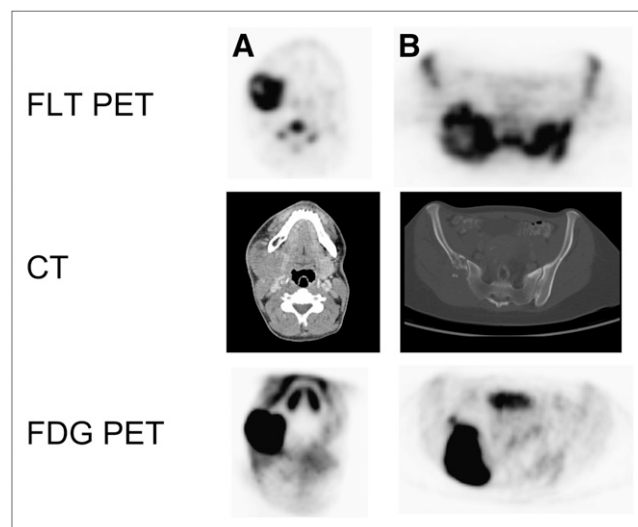
### Correlation of Initial $^{18}\text{F}$ -FLT Uptake with Response

$^{18}\text{F}$ -FLT PET was performed successfully in all 66 patients (Fig. 1). All  $^{18}\text{F}$ -FLT PET scans were visually rated as positive, resulting in a detection rate of 100%. Mean

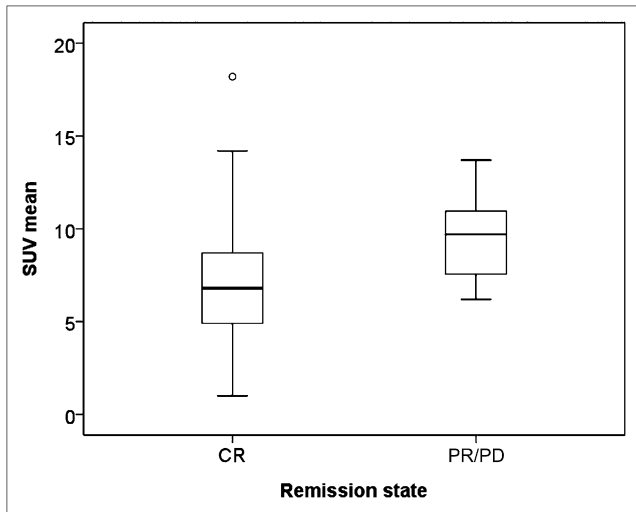
uptake of  $^{18}\text{F}$ -FLT in lymphoma manifestations (mean FLT SUV) was 7.3 (range, 1.0–18.2). Corresponding maximum  $^{18}\text{F}$ -FLT uptake ranged from 1.2 to 20.4, resulting in a mean  $\text{SUV}_{\text{max}}$  of 9.4. To determine the predictive value of pretreatment  $^{18}\text{F}$ -FLT uptake,  $^{18}\text{F}$ -FLT SUVs were correlated with treatment response. Because of the low number of patients with PR and PD, the initial  $^{18}\text{F}$ -FLT uptake was compared for patients in CR ( $n = 55$ ) and with patients in non-CR ( $n = 7$ ). The initial mean  $\text{SUV}_{\text{mean}}$  was significantly lower for patients achieving a CR (mean  $\text{SUV}_{\text{mean}}$ , 7.1; range, 1.0–18.2) than for patients not achieving CR (mean  $\text{SUV}_{\text{mean}}$ , 9.5; range, 6.2–13.7,  $P = 0.049$ ) (Fig. 2). Thus, pretreatment  $^{18}\text{F}$ -FLT PET  $\text{SUV}_{\text{mean}}$  may predict CR achievement. The same tendency, but without statistical significance ( $P = 0.218$ ), was observed for  $\text{SUV}_{\text{max}}$ , which showed lower values for patients achieving CR (mean  $\text{SUV}_{\text{max}}$ , 9.4; range, 1.2–20.4) than for patients not achieving CR (mean  $\text{SUV}_{\text{max}}$ , 11.0; range, 7.0–16.4).

### Correlation of Initial $^{18}\text{F}$ -FLT Uptake with IPI Score and Proliferation Index

The IPI is the main prognostic tool for survival in patients with DLBCL. This score ranges from 0 to 5 points, comprising 4 risk groups (15). For correlation with the initial  $^{18}\text{F}$ -FLT uptake, IPI score subgroups were formed with scores of 2 or less (low and low-intermediate risk) and more than 2 (high-intermediate and high risk). For both  $\text{SUV}_{\text{mean}}$  and  $\text{SUV}_{\text{max}}$ ,  $^{18}\text{F}$ -FLT uptake was significantly



**FIGURE 1.** Transaxial views of  $^{18}\text{F}$ -FLT PET, helical CT, and  $^{18}\text{F}$ -FDG PET for 2 patients with DLBCL. (A) A 41-y-old man with retro-mandibular lymphoma showing intense  $^{18}\text{F}$ -FDG and  $^{18}\text{F}$ -FLT uptake in projection of retro-mandibular lymph node. This stage IA patient revealed PD under therapy. (B) A 40-y-old woman (stage IVA) with histologically proven lymphoma in right iliac bone and sacrum.  $^{18}\text{F}$ -FDG PET shows intensely increased uptake in right ilium and sacrum. Corresponding  $^{18}\text{F}$ -FLT PET images allow detection of increased asymmetric uptake in right ilium and sacrum despite high physiologic  $^{18}\text{F}$ -FLT uptake in proliferating bone marrow. Transaxial views of helical CT display osteodestruction of right ilium. Restaging after end of therapy revealed CR.



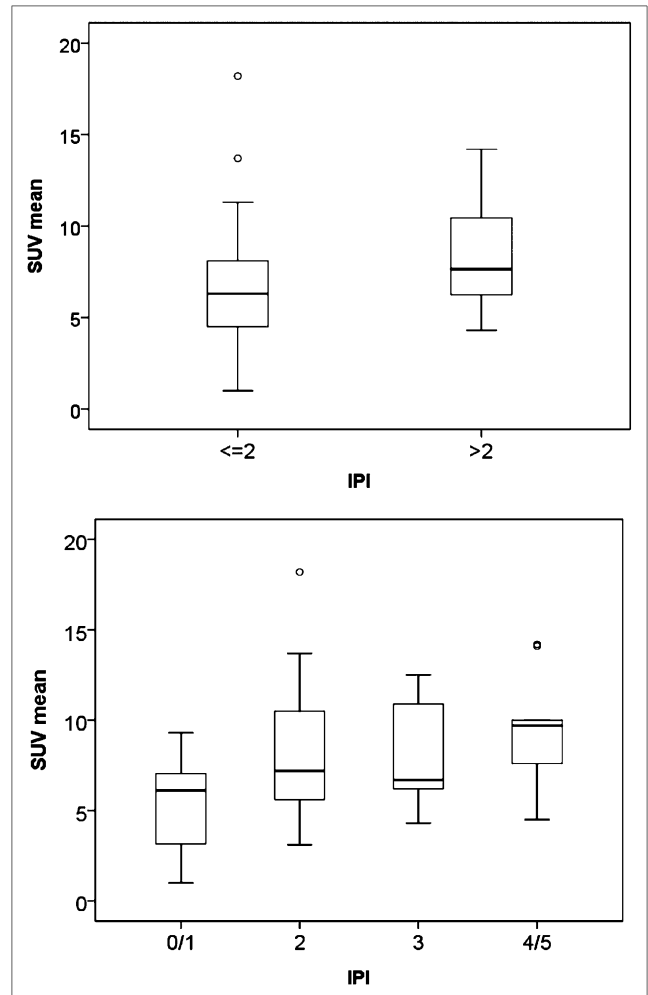
**FIGURE 2.** Initial  $^{18}\text{F}$ -FLT uptake ( $\text{SUV}_{\text{mean}}$ ) in patients achieving CR vs. patients with PR or PD ( $P = 0.049$ ; difference in median values, 2.5 [95% CI, 0.0–5.2]).

lower in the subgroup with an IPI score of 2 or less than in the group with an IPI score of more than 2 ( $\text{SUV}_{\text{mean}}$ , 6.6 vs. 8.6;  $P = 0.012$ ;  $\text{SUV}_{\text{max}}$ , 8.7 vs. 10.7;  $P = 0.002$ ). In addition, trend analysis revealed a significant positive relationship between  $\text{SUV}_{\text{mean}}$  levels and IPI risk groups (Spearman  $\rho$ , +0.44,  $P < 0.001$ ) (Fig. 3). Similar results were found for  $\text{SUV}_{\text{max}}$  (Spearman  $\rho$ , +0.41,  $P < 0.001$ ).

Ki67 immunohistochemistry could be performed in 43 of 66 patients. Ki67-positive lymphoma cells ranged between 35% and 95% (mean,  $67\% \pm 17\%$ ; median, 70%). Correlation analysis between initial  $^{18}\text{F}$ -FLT uptake and Ki67 proliferation index showed a tendency to higher Ki67 proliferation rates in patients with higher initial  $^{18}\text{F}$ -FLT uptake. However, no statistical significance was found (Spearman  $\rho$ , 0.21;  $P = 0.18$ ). Also, Ki67 immunoreactivity in lymphoma specimens of patients achieving CR and patients with non-CR was not significantly different ( $P = 0.61$ ; median for CR: 70%, range, 35%–95%, vs. median for non-CR: 73%, range, 60%–85%).

#### Prognostic or Predictive Value of Initial $^{18}\text{F}$ -FLT Uptake with Regard to Survival

Follow-up was available in 62 patients. The median follow-up was 18.1 mo (mean, 22.6 mo; range, 1.1–63.1 mo). During this interval, 4 patients experienced recurrence and 8 patients died. Lymphoma-associated death was found in 3 patients. Martingale residual analysis was performed for all 8 death events but revealed no relevant correlation between survival and initial  $^{18}\text{F}$ -FLT uptake (Fig. 4B). The corresponding estimated hazard ratio per 1-point increment of  $^{18}\text{F}$ -FLT  $\text{SUV}_{\text{mean}}$  was 1.03 (95% CI, 0.83–1.27,  $P = 0.80$ ). However, initial  $\text{SUV}_{\text{mean}}$  was significantly higher in the 3 patients with lymphoma-associated deaths (mean, 11.1; range, 9.7–13.7) than in those with non-lymphoma-associated deaths (mean, 6.6; range, 4.5–7.5;  $P = 0.036$ ) or in all included patients (mean, 7.3;  $P = 0.034$ ). Thus, high

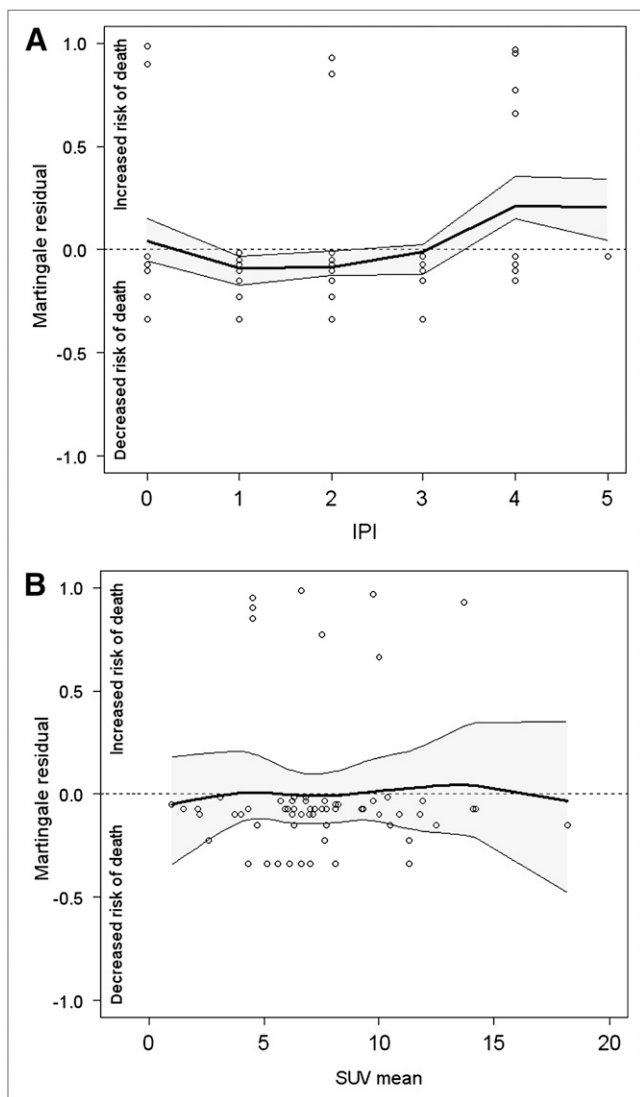


**FIGURE 3.** Initial  $^{18}\text{F}$ -FLT uptake ( $\text{SUV}_{\text{mean}}$ ) in patients with IPI score lower than or equal to 2, compared with patients with IPI score greater than 2 ( $P = 0.012$ ; difference in medians, 2.1 [95% CI, 0.5–3.7] (top). Trend analysis of initial  $^{18}\text{F}$ -FLT uptake ( $\text{SUV}_{\text{mean}}$ ) with IPI risk groups (Spearman  $\rho$ , +0.44,  $P < 0.001$ ) (bottom).

initial  $^{18}\text{F}$ -FLT uptake might be used as a surrogate marker for prediction of unfavorable outcome under R-CHOP chemotherapy.

#### Association of IPI Score, Response, and Survival

Because the IPI score is the standard prognostic tool for survival in DLBCL patients, we tested the predictive value of the IPI score regarding response to therapy in our patient population. Similar to initial  $^{18}\text{F}$ -FLT uptake, the IPI score revealed a statistically significant difference between patients in CR and non-CR. Patients achieving CR had a significantly lower IPI score (median, 2; range, 0–5) than patients rated as PD or PR (median, 4; range, 0–4) ( $P = 0.039$ ). In contrast, Martingale residual analysis revealed no relevant association between IPI score and risk of death (Fig. 4A). The corresponding estimated hazard ratio per 1-point increment of IPI score was 1.43 (95% CI, 0.81–2.52,  $P = 0.22$ ). Taken together, these data demonstrate



**FIGURE 4.** (A) Martingale residual analysis of IPI score and risk of death. Solid lines depict smoothing spline function, with simultaneous 95% confidence bands. Three patients with lymphoma-associated death had IPI scores of 2, 4, and 4. Corresponding estimated hazard ratio per 1-point increment of IPI score was 1.43 (95% CI, 0.81–2.52,  $P = 0.22$ ). (B) Martingale residual plots of overall survival and initial  $^{18}\text{F}$ -FLT uptake. Solid lines depict smoothing spline function, with simultaneous 95% confidence bands. Corresponding estimated hazard ratio per 1-point increment of  $^{18}\text{F}$ -FLT SUV<sub>mean</sub> was 1.03 (95% CI, 0.83–1.27,  $P = 0.80$ ). Initial  $^{18}\text{F}$ -FLT uptake was significantly higher in 3 patients with lymphoma-associated death (mean, 11.1; range, 9.7–13.7) than in those with non-lymphoma-associated deaths (mean, 6.6; range, 4.5–7.5;  $P = 0.036$ ) and in whole study cohort (mean, 7.3;  $P = 0.034$ ).

that both the well-established IPI score and the initial  $^{18}\text{F}$ -FLT uptake were able to predict treatment outcome in our study.

## DISCUSSION

$^{18}\text{F}$ -FLT has been demonstrated to reflect proliferation-dependent retention of nucleosides in malignant lymphoma, which can be assessed noninvasively by PET (13). How-

ever, the predictive and prognostic potential of pretherapeutic imaging using  $^{18}\text{F}$ -FLT remains to be determined. To the best of our knowledge, this is the first study investigating the predictive value of  $^{18}\text{F}$ -FLT PET regarding response to treatment and survival in aggressive B-cell non-Hodgkin lymphoma. Compared with patients not achieving a CR (the PR/PD group), patients who achieved CR with R-CHOP treatment, as assessed by well-established response criteria, had a significantly lower SUV<sub>mean</sub>  $^{18}\text{F}$ -FLT uptake before treatment. This might indicate that a higher proliferation rate, as measured by  $^{18}\text{F}$ -FLT PET, is a negative predictor regarding CR. Regarding SUV<sub>max</sub>,  $^{18}\text{F}$ -FLT uptake was also higher in the PR/PD group than in the CR group; however, the difference was not statistically significant, presumably because of the low number of treatment failures in our study cohort. Quite notably, among the deceased patients, the 3 patients who died from progressive lymphoma showed the highest  $^{18}\text{F}$ -FLT uptake values (SUV<sub>mean</sub>, 9.7, 10.0, and 13.7). This result thus indicates that  $^{18}\text{F}$ -FLT PET may identify a poor prognostic subgroup. It is tempting to speculate that  $^{18}\text{F}$ -FLT uptake correlates with a poor-outcome subgroup that has been identified in molecular studies using gene expression technologies (22,23). Overall, the response rate in our patient population was rather high (CR in 55/66 patients)—partly explained by the fact that the  $^{18}\text{F}$ -FLT PET scanning prolonged the diagnostic work-up, resulting in a delay of treatment initiation. Accordingly, patients who were considered to require immediate therapy by the treating clinician and patients with reduced performance status may be underrepresented in this study.

Our data clearly show that the initial  $^{18}\text{F}$ -FLT uptake significantly correlates with the IPI score ( $P = 0.049$ ) and response to treatment. IPI score, representing the best prognostic indicator for survival, was able to predict achievement of CR versus non-CR in our study (15). This observation further underlines the potential of *in vivo* proliferation imaging and provides evidence for  $^{18}\text{F}$ -FLT uptake as a predictive tool comparable to the well-established IPI score. However, prediction of survival is clinically more relevant than prediction of response to treatment. Because of the low number of events, we could not show a predictive relevance of the initial  $^{18}\text{F}$ -FLT uptake for survival in this study. However, these findings are encouraging and warrant analysis in a larger cohort. In a small study with 20 head and neck cancer patients, it was also shown that initial  $^{18}\text{F}$ -FLT and  $^{18}\text{F}$ -FDG uptake correlates with survival (24). Besides these limited data, correlation of initial  $^{18}\text{F}$ -FLT uptake and survival has not yet been studied in other tumor entities.

Nearly all patients presented with intense uptake of the radionucleoside  $^{18}\text{F}$ -FLT, and all of the lymphoma lesions identified by conventional imaging modalities (spiral CT,  $^{18}\text{F}$ -FDG PET/CT) were visible by  $^{18}\text{F}$ -FLT PET. The high sensitivity for detection of aggressive lymphoma is in agreement with several previously published trials (6,10,13,25,26). Even osseous lesions were detectable

because of focal  $^{18}\text{F}$ -FLT uptake greater than the surrounding bone marrow. However, it has been reported previously that the sensitivity of  $^{18}\text{F}$ -FLT PET in tissues with high physiologic  $^{18}\text{F}$ -FLT uptake (e.g., bone marrow or liver) is lower than that of  $^{18}\text{F}$ -FDG PET or conventional imaging procedures (6). Our study is by far the largest clinical trial using  $^{18}\text{F}$ -FLT PET for the characterization of aggressive lymphoma ( $n = 66$ ). A major strength of our study is a high number of patients assessed who demonstrated that proliferation imaging is a sensitive and reliable procedure potentially suitable also for initial staging of aggressive B-cell lymphoma (6,25,26).

Before translating these results into clinical routine practice, several important limitations have to be considered. First, in this study only 8 patients died during follow-up, and only 3 deaths were lymphoma-associated. This favorable prognosis of patients observed in our series requires confirmation of our data and our conclusions in a larger cohort. Second, this study investigated the prognostic relevance of only the initial  $^{18}\text{F}$ -FLT uptake without evaluating changes in  $^{18}\text{F}$ -FLT uptake during the course of the treatment, which might represent a better predictive tool. A clear advantage for  $^{18}\text{F}$ -FLT, compared with the standard tracer  $^{18}\text{F}$ -FDG, is its higher specificity for malignant tumors (7).  $^{18}\text{F}$ -FDG PET allows the imaging of increased consumption of glucose, which is a characteristic of most tumor cells and is partially related to overexpression of the glucose transporter type 1 and increased hexokinase activity (27). However, the specificity is reduced because of physiologic glucose uptake in brown fat tissue, colonic and gynecologic activity, infections and inflammations, and rebound thymic hyperplasia. Nonspecific  $^{18}\text{F}$ -FDG accumulation in inflammatory lesions is of major importance for therapy monitoring. Overestimation of  $^{18}\text{F}$ -FDG uptake might occur in tumors with an inflammatory component or, more often, might occur because of chemotherapy- or radiation-mediated inflammatory processes. This unspecific uptake may persist for weeks or months, potentially influencing the assessment of changes in glucose metabolism during therapy response assessment (28). Moskowitz et al. demonstrated that most  $^{18}\text{F}$ -FDG-positive lesions detected by interim PET were negative as determined by repeated biopsy (4). These limitations of  $^{18}\text{F}$ -FDG PET strongly indicate potential applications for  $^{18}\text{F}$ -FLT, which seems to be more specific than  $^{18}\text{F}$ -FDG. Although false-positive findings have been reported also for  $^{18}\text{F}$ -FLT PET caused by proliferating lymphocytes in reactive lymph nodes,  $^{18}\text{F}$ -FLT might be suitable or even superior to  $^{18}\text{F}$ -FDG for monitoring response to treatment, particularly in the setting of interim PET analyses (29).

## CONCLUSION

Our data demonstrate that  $^{18}\text{F}$ -FLT PET is a promising and sensitive tool for the detection of lymphoma lesions and for predicting response to treatment in aggressive B-cell lymphoma. In addition, we found a significant cor-

relation of  $^{18}\text{F}$ -FLT uptake and the IPI score, which still represents the main prognostic tool in DLBCL. Our current data clearly justify further evaluation in larger cohorts to confirm initial or interim  $^{18}\text{F}$ -FLT PET as a predictive tool in the management of DLBCL patients.

## DISCLOSURE STATEMENT

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